Effects of diabetes mellitus regulation on antibody response to inactivated virus vaccine: a systematic review

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ABSTRACT

Background: Diabetes mellitus (DM) could hamper the immune responses, including that induced by the vaccine. The aim of this study was to evaluate the immunogenicity of coronavirus disease 2019 (COVID-19) inactivated vaccines in patients with DM either controlled or uncontrolled through a systematic review approach.

Methods: Without regard to time constraints, searches were conducted in ProQuest, Embase, and PubMed to assess the available data on the impact of DM regulation on the immunogenicity of post-vaccinated DM patients. The PRISMA guideline and the PICO criteria were used. The quality of studies was assessed using the National Institutes of Health (NIH) quality assessment tool. There is not enough Available data comparing the immunogenicity of the vaccine in controlled and uncontrolled DM patients is limited.

Results: Out of 20,657 articles, five studies were included, of which three had good quality and two had fair quality. Our data suggested that DM patients vaccinated with CoronaVac/SinoVac had lower seroconversion rates significantly lower compared to those without DM. The immunogenicity of BBV-152 vaccine in DM patients was also significantly lower than in patients without DM. Studies comparing the immunogenicity of the vaccine between controlled and uncontrolled DM patients are limited.

Conclusion: Patients with DM have lower antibody levels than non-DM patients who received inactivated COVID-19 vaccines. Glycemic management has emerged as critical to maximizing the immunogenicity induced by inactivated vaccines in a small number of patients; however, to support this conclusion, studies with adequate number of patients are critical.

Keywords: COVID-19, SARS-CoV-2, diabetes mellitus, vaccination, immunogenicity.


BACKGROUND

The coronavirus disease 2019 (COVID-19) is a significant health problem.1-4 Diabetes mellitus (DM) is a significant health problem globally with high morbidity and mortality rates.5 Inflammation, stimulation of the renin-angiotensin-aldosterone system (RAAS), modifications in glucose hemostasis, and immunological response are expected as pathophysiologic mechanisms of how DM influences the COVID-19.5 Prevention measures is one of the main objectives in DM patients due to limited number of anti-COVID-19.5

As a group of people at high risk, individuals with DM should immediately receive the vaccination to gain immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus caused the COVID-19. Various vaccines have also been circulating worldwide, ranging from inactivated vaccine types (CoronaVac, Sinopharm, COVAXIN (BBV152)), vector-based vaccines (AZD1222 (ChAdOx1), Sputnik V (GamCOVIDVac)), to mRNA-based vaccines (mRNA-1273 and BNT162b2).7-12 The inactivated vaccine usage has been used in more than 50 countries in the world, making inactivated vaccines one of the most widely distributed vaccine types in the world.13-14 It is important to determine the efficacy of vaccines in special populations such as among those with DM so that new policies can be formulated to maximize vaccine efficacy if needed.

The aim of this study was to determine the impact of DM regulation on the immunogenicity of post-vaccinated DM patients using a systematic review. These data are essential to determine whether there is a difference in the benefits and risks of administering the vaccine in uncontrolled DM patients.

METHODS

Study design
A systematic review was conducted to assess the available data on the impact of DM regulation on the immunogenicity of post-vaccinated DM patients. We followed the PRISMA guideline during the study and during the reporting process. The PICO criteria for the individuals, studies, interventions, and outcomes were also used.

Search strategy
PubMed, Embase, and ProQuest data bases were searched for relevant articles published up to October 1, 2022, matching the PICO question using the keywords:

Eligibility criteria
All studies assessing the immunogenicity of COVID-19 vaccine in DM patients were considered eligible. The inclusion requirements are followed: (1) Population: studies involving individuals who have diabetes and whose condition has been diagnosed using the ADA criteria; (2) Intervention: immunization against COVID-19 with inactivated type vaccines (SinoVac, CoronaVac, Sinopharm, Ad5-nCoV, BBV152); (3) Study design: clinical trials, retrospective studies, and prospective studies; (4) Results: both patients with controlled and uncontrolled diabetes and vaccine immunogenicity was the primary finding. The proportion of vaccine recipients who experienced positive seroconversion was used to define immunogenicity. All literature reviews, editorial and personal viewpoints, and non-English-written articles were excluded.

Data Collection
Two investigators independently examined all relevant studies. The following information was collected from all included articles: author name, title, date of publication, nation of origin, study design, the number of patients during the initial and follow-up, patient age, and the sex ratio, complications of DM, and immunogenicity of the vaccine. In case of disagreements between two investigators, the third expert made the consensus.

Quality assessment
The quality of included studies was assessed using a quality assessment tool from the National Institutes of Health (NIH). Each study was determined as low, fair, and excellent quality for that the scored of 0-5, 6–10, and 11–14, respectively.

RESULTS
Results of study selection and study characteristics
The database searches resulted 20657 hits of which 20444 were excluded after assessing the title and abstract. After carefully reviewing the remaining 80 papers, five studies fulfilled the inclusion requirements and were included.

The study selection processes’ steps are presented in Figure 1.

Studies that were included were published between 2021 and 2022. The studies’ samples ranged from 86 to 4626 people and the mean ages of the participants ranged from 37 to 70 years old. Three studies lacked controls, and two studies had the controls. Only one study mentioned the type of diabetes. Four studies examined the effectiveness of CoronaVac, Sinopharm, or Sinovac vaccines. BBV-152 vaccine was evaluated in one study. The details of the included studies are presented in Table 1.

Quality assessment of the studies
The quality assessment of the included studies are presented in Table 2. Two studies had fair quality, while three studies had good quality.

Immunogenicity of the vaccines
In four studies examining the seroconversion rates of DM patients vaccinated with CoronaVac/ SinoVac, three studies found that the seroconversion rates were significantly lower in DM patients. A study by Güzel et al. showed a significantly lower of IgG seroconversion rate (p<0.001) in DM patients three weeks after the second dose. The same results were found in the Karamese et al. study where the antibody response was also significantly lower (p<0.001). The study in Chile also showed a significantly lower number of IgG seropositivity in DM patients (p<0.001). However, a study of Alqassieh...
### Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>DM patients</th>
<th>Control patients</th>
<th>Mean age (year)</th>
<th>Male proportion (%)</th>
<th>Type of DM</th>
<th>Type of vaccine</th>
<th>Antibodies outcome</th>
<th>Follow-up period</th>
<th>Dose</th>
<th>Number of days between doses</th>
<th>Cut-off for positive seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alqassieh et al. 2021&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Jordan</td>
<td>Prospective cohort</td>
<td>76</td>
<td>NA</td>
<td>NA</td>
<td>65.6</td>
<td>NA</td>
<td>BNT162b2 Sinopharm</td>
<td>IgG IgM</td>
<td>6 weeks</td>
<td>2</td>
<td>21 days</td>
<td>Index ≥ 1 (index was a ratio between the relative fluorescence value measured in the sample and calibrator)</td>
</tr>
<tr>
<td>Güzel et al. 2021&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Turkey</td>
<td>Prospective cohort</td>
<td>80</td>
<td>103</td>
<td>37.2</td>
<td>46.4</td>
<td>NA</td>
<td>CoronaVac SinoVac</td>
<td>IgG</td>
<td>21 days</td>
<td>2</td>
<td>28 days</td>
<td>Arbitrary units (AU) &gt; 1.1</td>
</tr>
<tr>
<td>Saure et al. 2021&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Chile</td>
<td>Surveillance study</td>
<td>4626</td>
<td>NA</td>
<td>NA</td>
<td>41.1</td>
<td>NA</td>
<td>CoronaVac BNT162b2</td>
<td>IgG IgM</td>
<td>16 weeks</td>
<td>2</td>
<td>NA</td>
<td>Visible bands on the IgG and test control position</td>
</tr>
<tr>
<td>Singh et al. 2021&lt;sup&gt;20&lt;/sup&gt;</td>
<td>India</td>
<td>cross-sectional</td>
<td>57</td>
<td>495</td>
<td>44.8</td>
<td>59.2</td>
<td>T2DM</td>
<td>ChAdOx1-nCoV BBV-152 CoronaVac</td>
<td>Anti-spike antibody IgG</td>
<td>6 months</td>
<td>2</td>
<td>NA</td>
<td>&gt;15.0 AU/mL</td>
</tr>
<tr>
<td>Karamese et al. 2022&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Turkey</td>
<td>cross-sectional</td>
<td>49</td>
<td>NA</td>
<td>70.3</td>
<td>52.8</td>
<td>NA</td>
<td>CoronaVac</td>
<td>Anti-SARS-CoV-2 antibody</td>
<td>4 weeks</td>
<td>2</td>
<td>NA</td>
<td>&gt;35.2 IU/ml</td>
</tr>
</tbody>
</table>

### Table 2. Critical appraisal of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total score</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
<th>Q9</th>
<th>Q10</th>
<th>Q11</th>
<th>Q12</th>
<th>Q13</th>
<th>Q14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alqassieh et al. 2021&lt;sup&gt;17&lt;/sup&gt;</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Güzel et al. 2021&lt;sup&gt;18&lt;/sup&gt;</td>
<td>10</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Saure et al. 2021&lt;sup&gt;19&lt;/sup&gt;</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Singh et al. 2021&lt;sup&gt;20&lt;/sup&gt;</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Karamese et al. 2022&lt;sup&gt;21&lt;/sup&gt;</td>
<td>9</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
et al. showed a non-significant difference of IgG levels between DM and non-DM patients.17

One study compared the BBV-152 vaccine (Covaxin) with a vector-based vaccine (ChAdOx1-nCoV) and showed that in both types of vaccine, the immunogenicity in DM patients was significantly lower than in patients without DM.20 A study compared the immunogenicity of inactivated vaccines with mRNA or vector-based vaccines in DM patients.19 The study found a significant difference of vaccine immunogenicity, where mRNA or vector-based vaccines had higher immunogenicity and seroconversion ratio than inactivated vaccines.19

Available data comparing the immunogenicity of the vaccine in controlled and uncontrolled DM patients is limited. Of the included studies, one study specifically compared the post-vaccination immunogenicity in controlled and uncontrolled DM patients.20 However, the number of the sample was very small; there were two uncontrolled DM patients and 55 controlled DM patients. In addition, this study also did not mention the parameters that classify as controlled and uncontrolled DM patients.20

**DISCUSSION**

With the emergence of various types of COVID-19 vaccines, vaccine immunogenicity has become an indicator of vaccine effectiveness in preventing severe COVID-19.22 The vaccine immunogenicity is generally measured by observing the neutralizing antibody and antibody binding after the vaccination dose is completed.23 The inactivated vaccine is one of the first vaccines developed during the COVID-19 pandemic. This vaccine has the advantage of milder side effects, but in general, the immunogenicity formed is lower than that of mRNA or vector-based vaccines.24,25

Several studies have shown that DM patients generally exhibit lower immunogenicity than patients without DM.26–28 This is related to the course of DM which impacts many factors. One of these factors is chronic low-grade inflammation in patients with high blood sugar levels. This affects the disruption of cell-mediated immune activation, such as macrophages and T cells, and an increase in proinflammatory cytokines beyond normal limits.26–28

The included five studies in this systematic review, all showed lower immunogenicity in patients with DM that were vaccinated with the inactivated type vaccine, four studies found significantly lower than patients without DM with the same vaccination.18–21 A study found no significant difference of IgG titers (p=0.085) between DM and non-DM patients after adjusting for other variables.17 In this study, the presence of cardiovascular disease was more significantly affected the post-vaccination titer.17 It should be noted that uncontrolled DM can progress to cardiometabolic disorders, such as hypertensive heart disease and congestive heart failure.29 Cardiovascular disease is independently related to a person’s immunity, which originates from a molecular mechanism in the form of endothelial dysfunction, thereby triggering low-grade inflammation and having an impact similar to DM.30 If a person has a cardiometabolic disorder, there is a possibility that person will experience a multiplier effect on decreased immunity and needs special attention.

Güzel et al. and Karamese et al. found that DM patients had lower mean titers of IgG than non-DM patients, but the seropositivity level remained above 95%.18,21 In addition to the effect of DM, IgG antibodies were also lower in older patients, overweight and obese, and those with a history of cardiovascular disease.18,21 Another study found that DM and chronic disease patients had lower seropositivity rates with the CoronaVac vaccination, but uniquely, the same was not found in DM and chronic disease patients vaccinated with the BNT162b2 vaccine.19 However, those aged 60 years or older had lower seropositivity than those aged 60 and under in both types of vaccines. This study also found decreased seropositivity after 5 months of follow-up in patients vaccinated with CoronaVac.19 The reduced immunogenicity in patients with inactivated vaccines may be related to low baseline immunogenicity at the outset. This is not the case with mRNA vaccines because mRNA vaccines have the advantage of increasing the body’s immunity from the side of molecular assembly, compared to other types of vaccines that rely on natural immunogenicity.31 Although the clinical trial found a plateau phase of antibody reduction after vaccination with CoronaVac,25 studies with longer monitoring times are needed to ascertain the durability of the inactivated vaccine to determine whether a person needs a booster vaccination.

A study also compared whether DM control affected post-vaccination antibody titers.20 However, due to the disproportionate comparison between controlled and uncontrolled DM patients, it cannot be concluded whether the inactivated vaccine has an effect or not. However, another study that examined DM control in patients after administration of a vector-based vaccine showed a significant inverse relationship between HbA1c levels with neutralizing antibody levels and the response to antigens from CD4+ cells.32 Another study by Sourij et al. found the same relationship with the previous study, but after adjusting for confounding variables, this result became insignificant.33

The effect of DM control in DM patients vaccinated with inactivated vaccines is still lacking in studies, although there is no real evidence that there is a hassle in controlling DM during the pandemic.34 However, studies found that patients with hyperglycemia had substantially lower immunity and the immune response with other vaccinations was lower.35–38 Although in general, the immunogenicity results in four of the five studies showed significant differences, this is still difficult to validate considering that the gold standard for immunogenicity of other vaccines is to look at neutralizing antibody activity, which none of the included studies measured. In addition, not all studies have considered other confounding factors to ascertain significance. The IgG assay performed in several studies was chosen because the results can be considered to reflect the immunogenicity response caused by the vaccine, but do not reflect the protection shown by neutralizing antibodies.

Vaccination with vector-based and mRNA-based vaccines also showed that
uncontrolled DM patients had lower seroconversion rates. This concludes that the quality of DM control needs to be considered to vaccinate DM patients to achieve maximum immunogenicity. Regardless of the quality of DM control, considering the inactivated vaccine is the vaccine that triggers the lowest immunogenicity when compared to vector or mRNA-based vaccines, booster vaccines are significant to be given to maintain immunogenicity in DM patients to avoid severe COVID-19 symptoms.

CONCLUSION

Our data suggest that the antibody levels in DM patients are lower than in non-DM patients with inactivated vaccination. In a limited number of studies, glycemic control has become important to maximize the immunogenicity triggered by inactivated vaccines. Given that many countries primarily use inactivated vaccines, studies examining in particular on immune response to inactivated vaccines should be required to strengthen this conclusion.

ETHICAL APPROVAL

Not required.

COMPETING INTERESTS

The authors declare no competing interest.

GRANT INFORMATION

None.

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AUTHOR CONTRIBUTION

All author had contributed to manuscript writing and agreed for the final version of manuscript for publication.

REFERENCES


